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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,085	12/10/2001	Solomon Langermann	10271-037-999	9514

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,085	LANGERMANN ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/04 & 4/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claims 1-21, and 33, in the reply filed on November 8, 2004 is acknowledged.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, figures 3, and 4 is a disclosure of nucleic and amino acid sequences, which are not identified by sequence identification numbers. There are many references to FimH and FimC proteins from *E. coli,* amino acid residues from, presumably, amino acid sequences, which are not identified by a sequence identification number. Rule 37 CFR 1.821 (d) states that:

> "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

Accordingly, applicants must insert a sequence identification number after each occurrence of FimH and FimC as well as identify the amino acid sequence from which an amino acid residue is cited in the text to perfect their compliance with 37 CFR 1.821(d).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example page 15, line 26, and page 103, lines 11 and 13. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

A substitute specification without the claims is required pursuant to 37 CFR 1.125(a) because there is a white vertical line in almost every page masking many letters, see the entire specification starting with page 1.

A substitute specification must not contain new matter. The substitute specification must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) and a statement that the substitute specification contains no new matter must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown.

The drawings are objected to under 37 CFR 1.83(a) because they fail to show what is being described in the specification, see Figure 2 description. Specifically, the examiner can't identify the gray part of the molecule from the black part. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-15 and 33 are directed to all possible crystals of a ternary complex comprising any FimC protein from any biological source and mutants thereof, FimH protein from any biological source and mutants thereof, and any mannopyranoside, presumably, any chemical compound containing a mannopyranoside moiety which may include mannose, oligosaccharides, polysaccharides from any natural or man-made source. Claim 33 is not even limited to mannopyranoside. The specification, however, only provides two single representative species of these crystals: (1) a monoclinic crystal comprising the ternary complex FimH of SEQ ID NO: 4, FimC of SEQ ID NO: 2, and D-mannose in space group C2 with unit cell dimensions a = 138.077 Angstrom, b = 138.130 Angstrom, 215.352 Angstrom, and beta = 90.005 degrees; and (2) Q133N mutant of FimH of SEQ ID NO: 4, FimC of SEQ ID NO: 2, and methyl-alpha-D-mannose in space group C2 with unit cell dimensions a = 138.349 Angstrom, b = 138.334 Angstrom, 213.212 Angstrom, and beta = 89.983 degrees presumably obtained under the conditions described at page 136, lines 3-11. There is no disclosure of any

particular relationship between the structure of the ternary complex and the crystallization conditions. The specification also fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the cell dimension cited in claim 9, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. The identification of FimC and FimH by sequence identification number and the mannopyranoside in the ternary complex as well as identifying the crystal by its space group C2 would obviate this rejection.

Claims 16-21 are directed to a method of obtaining any crystal of said ternary complex under any crystallization conditions, which include the crystallization of any ternary complex as cited above using any precipitant, at any pH, in any buffer system, at any protein concentration and temperature. The specification, however, only provides a single representative species of these crystallization conditions at page 136, lines 3-11. There is no disclosure of any particular relationship between the structure of the ternary complex and the crystallization conditions. The specification also fails to describe additional representative species of these crystallization conditions by any identifying compositions or properties other than those cell dimension cited in claim 9, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. Claims directed to the specific crystallization conditions described in section 6.6.2 at page 136 as well as identify FimH and FimC with sequence identification number would obviate this rejection.

Claims 1-21 and 33 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising a ternary complex consisting of any FimH from any biological source and mutants thereof, FimC from any biological source and mutants thereof and any mannopyranoside or saccharide as well as any method to obtain any crystals. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in

the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any method to obtain any crystal comprising a ternary complex consisting of any FimH and FimC proteins from any biological source and mutants thereof as well as any chemical compound comprising any saccharide or mannopyranoside. The specification provides guidance and examples in the form of an assay to crystallize the ternary complex of the FimH of SEQ ID NO: 4, and the FimC of SEQ ID NO: 2, both from *E. coli* in the presence of D-mannose or methy-alpha-D-mannose (see example 6). While molecular biological techniques and genetic manipulation to make any protein and synthetic method to make any saccharide and D-mannopyranoside are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form crystallizing is highly unpredictable. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space on board of a space shuttel, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallizable. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a FimH or FimC proteins from a biological source or their cystallizable mutants, a carbohydrate derivatives capable of forming a complex with FimHC and its mutants, and identify a crystal suitable structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions and mutants which can be crystallized, where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the FimH and FimC, the chemical structure of a saccharide or mannopyranoside which is capable to bind to the binary complex FimHC, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-21, and 33 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Knight *et al.* (IDS reference: Acta Cryst. 1997, D53, 207-210).

Knight *et al.* disclose a crystallization method and a crystal of the chaperon-adhesion complex (FimC-FimH) from *Eschirichia coli*, see the abstract. They teach that the amino acid sequence for both FimC-FimH are known in the prior art, see page 206, last paragraph, and the purification of FimC-FimH complex by mannose affinity column eluted with methyl-alpha-mannopyranoside, see page 208, second paragraph. Also, they teach crystallization method for the binary complex using the hanging drop method under conditions comprising 0.4-1.1 M ammonium sulfate precipitant in 100 mM Tris-HCl buffer, pH 8.3, said method produced a diffraction quality crystal, see the paragraph bridging the right and left column at page 208. Further, they reported an isomorphous crystal of selenomethionylated Fim-FimH (heavy atom derivative), and significant improvement in the size and quality of the crystal by addition of carbohydrate to the crystallization medium; see the crystal in Figure 1(b). It is pointed out that all of the additives that result in improved crystal quality have structure features in common with the mannose receptor, and thus, concluded that the improvement is due to binding of the carbohydrate additive in the receptor binding pocket, see page 209, right column, fourth paragraph. Finally, Knight *et al.* report the unit cell dimension of a crystal comprising the binary complex FimC-FimH, but does not report any unit cell dimension for crystals that was stabilized and improved by the addition of carbohydrate compounds such as that shown in Figure 1 (b).

The crystals described on page 209, right column, fourth paragraph, of which one of them shown in Figure 1 (b), appear to contain a ternary complex consisting of FimC-FimH and a compound containing a mannose moiety produced by the method described above which appear to be identical to the claimed method (claims 1, 6-8, 10-13-21, and 33). While Knight *et al.* do not teach unit cell dimension of a ternary complex, the unit cell dimensions of the crystals grown in the presence of carbohydrate derivatives reported by Knight *et al.* are an intrinsic properties of those crystals (claim 9). Later, structure determination of one of the crystal by X-ray crystallography shows a ternary complex, see IDS reference: Choudhury *et al.* Science 1999, 285, pages 1061-1066, in particular, page 1062 starting in the middle column, last paragraph. Interestingly, the crystal used by Choudhury *et al.* is made according to the method described by Knight *et al.* and has the C2 space group with close unit cell dimension, the legend for Table 1. It should be noted that Knight *et al.* provide motivation to one of

ordinary skill in the art to obtain a crystal grown in the presence of mannose or mannose derivatives as they teach the improvement of the quality of the crystal in the presence of carbohydrate compounds sharing structure similarity to mannose receptor.

These rejections are being made under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 because it is not possible for the examiner to physically compare the claimed crystalline complex and method of crystallization, and those crystalline complex reported and method of crystallization by Knight *et al.* Applicant bears the burden of providing evidence, which distinguishes the claimed crystalline complex from those disclosed by Knight *et al.* A preferred means of providing this evidence is for applicant to submit a side-by-side comparison between the crystallization method and crystals of the prior art and the claimed crystals and crystallization methods which demonstrates any material differences and shows the claimed crystal and crystallization method to be distinct and unobvious in view of the crystals and crystallization method of the prior art. *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald, Sanders and Bagheri* 205 USPQ 594 (CCPA 1980).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N-Shed

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652